963-19 Evidence for Complement Activation by Smooth Muscle Cells in Lesions of Advanced Pulmonary Hypertension (PH)

Vera D. Aiello, Maria L. Higuchi, Antonio A. Lopes, Fulvio Pileggi, Peter Libby [1]. *Heart Institute of São Paulo University, Brazil; [1] Brigham and Women's Hospital, Boston, MA*

In PH and other vascular obstructive diseases, the mediators of intimal hyperplasia of arteries have been extensively studied. Little attention has been given to the pathogenesis of the more advanced pulmonary vascular lesions, such as fibrinoid necrosis and plexiform lesions. Recently, it was shown that the membrane attack complex of the complement (MAC) plays a role in pathologic processes chracterized by cell proliferation, including atherosclerosis. To contribute to the understanding of the development of the arterial obstructive lesions in PH, we studied the expression of MAC in lungs from 8 patients presenting advanced vascular disease: five with primary PH, two with PH secondary to Schistosomiasis and one secondary to a congenital heart defect (mean age 20; median 17.5 years). We characterized immunohistochemically the proliferative vascular lesions using antibodies that recognize the active form of MAC, α-actin and Factor VIII, in paraffin embedded tissue. The intimal lesions, including plexiform lesions, contained predominantly α-actin positive smooth muscle cells (SMC). Factor VIII strongly labelled the endothelial cells of arteries, including the vascular spaces within plexiform lesions. All 8 cases exhibited positive MAC reaction (mild to moderate) in the medial layer of arteries but not of veins, staining individual SMC and also lining the internal and/or external elastic membranes. MAC was constantly negative in the SMC of the plexiform lesions and in endothelial cells. In only 2 of 8 cases was MAC expressed (weakly) in intimal lesions. MAC was also positive focally in fibrinoid necrosis. We conclude that SMC are the main constituents of the intimal and plexiform lesions, and that MAC is always present in the medial SMC. Since MAC is known to induce cell proliferation, our findings may suggest that it participates in the pathogenesis of obstructive lesions in human PH, and that the fibrinoid necrosis of the arterial wall could be related to a complement attack which extends beyond the sublytic stage.

963-20 MM-LDL Induced Monocyte Binding to HAEC is Mediated by Alpha-4 Chain of VLA-4 but not by VCAM-1

Devendra Vora, Farhad Parhami, Mary Territo, Judith A. Berliner. *Departments of Medicine & Pathology, UCLA Medical Center, Los Angeles, CA*

One of the early events in atherosclerosis is adhesion and transmigration of mononuclears into the subendothelium of large arteries. This localized mononuclear recruitment is probably caused by specific leucocyte adhesion molecules expressed by the endothelial cells at these sites. Oxidized LDL has been found to be present in fatty streaks and is suspected to be the cause of progression to a complicated lesion. It has been recently suggested that this selective adhesion of mononuclears is mediated by VCAM-1 expressed by the endothelial cells. Our group has shown that mildly oxidized LDL (MM-LDL) and not highly oxidized LDL (OX-LDL) induces a selective mononuclear binding to human aortic endothelial cells (HAEC) in culture (12). In our effort to further characterise the molecules involved in this adhesion we treated HAEC with MM-LDL for 6 hours and found an increase in monocyte binding by 158 monos/field +13 (177%) over background binding. An adhesion blocking VCAM-1 antibody (4B9) did not inhibit MM-LDL induced monocyte binding. However a blocking antibody to the alpha 4 chain of VLA-4 (L25.3) significantly reduced this binding to 24 monos/field +7 (26.6%) over the background binding. An antibody to the beta 1 chain of the VLA 4 (PSD2) reduced this binding to 75 monos/field +5 (93.9%) over the background. The antibody to beta 2 integrin (TS1/18) had no effect on this binding. These data suggest that MM-LDL induced monocyte binding to HAEC is mediated by the alpa 4 chain of the monocyte VLA-4 integrin, the endothelial ligand for which remains to be determined.

963-21 Primary Angioplasty Minimizes Reperfusion Injury and Enhances Recovery of Myocardial Function Compared with Thrombolysis

Yoshio Ohnishi, Jeffrey E. Saffitz, Burton E. Sobel, Peter B. Corr, James A. Goldstein. *Washington University, St. Louis, MO; William Beaumont Hospital, Royal Oak, MI*

This study was designed to determine whether recanalization of thrombotic coronary occlusions by primary angioplasty exerts effects on ischemic myocardium different from those elicited by thrombolysis. Accordingly, we characterized the effects on RV myocardium of 1 hr of thrombotic RCA occlusion, followed by 1 hr of reperfusion induced by pharmacologic regimens associated with a systemic lyric state (Group 1: SK 8000 U/kg, n = 5; or t-PA 1 mg/kg, n = 5) or primary angioplasty (Group 2, n = 5). Occlusion depressed RV free wall (FW) function by echo in both groups [systolic shortening (SS), Group 1 from 4.4 ± 0.4 to −3.2 ± 0.4 mm*, Group 2 from 6.3 ± 1.3 to −2.6 ± 0.7 mm*]. Thrombolytic reperfusion (mean occlusion duration = 70 min) led to abrupt RVFW swelling (echo diastolic thickness from 5.2 ± 0.3 to 8.4 ± 0.9 mm*) associated with diminished dyskinesis but minimal recovery of RVFW contraction (SS from −3.2 ± 0.4 to −0.7 ± 1.0 mm*); microscopy showed marked edema, contraction band necrosis and hemorrhage, indicative of reperfusion injury. In contrast, reperfusion by primary angioplasty (occlusion duration = 69 min) led to striking recovery of RVFW contraction function (SS from −2.6 ± 0.7 to 3.9 ± 1.3 mm*, **) with minimal reperfusion injury, i.e. only slight RVFW swelling by ultrasound (diastolic thickness 5.5 ± 0.2 to 6.3 ± 0.4 mm*, **) and edema without contraction bands or hemorrhage by microscopy. Thus, compared to thrombolysis, coronary recanalization by primary angioplasty limits reperfusion injury and enhances recovery of myocardial function (differences within group *, between groups **, $P < 0.05$).

963-22 Gene Knockouts for Neuronal Nitric Oxide Synthase Demonstrate Compensatory Mechanisms of Cerebrovascular Blood Flow Regulation

Paul L. Huang, Katsumi Irikura, Jianya Ma, Won Suk Lee, Turgay Dalkara, Mark C. Fishman, Michael A. Moskowitz. *Cardiovascular Research Center and Stroke Research Laboratory, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

We have investigated the role of nitric oxide as a mediator of the cerebrovascular blood flow response to hypercapnia in wild-type mice and knock-out mice that lack the neuronal nitric oxide synthase (NOS) gene. Mice were anesthetized, intubated, and ventilated. Baseline measurements of arterial blood pressure, end-tidal CO2, and blood gases were monitored, and were comparable in both groups of mice. Relative cerebral blood flow (rCBF) was measured by lased Doppler flowmetry. Hypercapnia induced by inhalation of 5 and 10% CO2 resulted in a 38 ± 15 and 77 ± 34% increase in rCBF in both the mutant and wild-type mice. Superfusion with nitro-L-arginine (L-NA) markedly attenuated the rCBF response in wild-type mice, but did not affect the response in the knock-out mice. Brain cGMP levels increased in response to hypercapnia in the wild-type animals, but not in the knock-out animals. Endothelium dependent dilation to topical acetylcholine was completely blocked by topical L-NA in both groups, demonstrating that endothelial NOS is not involved in the preserved hypercapnic response in the knock-out animals.

Based on these data, we conclude that (1) nitric oxide is not the sole mediator of the hypercapnic blood flow response, (2) neuronal NOS, and not endothelial NOS, contributes to hypercapnic hyperemia, (3) in the knock-out animals, mechanisms that do not involve nitric oxide or cGMP compensate for lack of the neuronal NOS gene to preserve the hypercapnic cerebrovascular blood flow response.

TUESDAY PM

964 Cardiovascular Therapeutics

Tuesday, March 21, 1995, Noon–2:00 p.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: 1:00 p.m.–2:00 p.m.

964-8 Oral Loading with Propafenone in Recent-Onset Atrial Fibrillation: A Controlled Evaluation on 240 Patients

Alessandro Capucci, Giuseppe Boriani, G. Luca Botto [1], Ida Rubino [2], Camillo Falcone [1], Stefano Della Casa [2], Mario Sanguinetti [2], Bruno Magnani. *Inst. of Cardiology, University of Bologna, Italy; [1] Dept. of Cardiology, Fatebenefratelli Hosp. Erba Como, Italy; [2] Dept. of Cardiology Civil Hops. Lugo, Ravenna, Italy*

Aim of this placebo-controlled study was to assess efficacy and safety of an acute oral loading of propafenone (PFN) in converting recent-onset atrial fibrillation (AF) (≤7 days duration) to sinus rhythm (SR). Two hundred fourty hospitalised patients, NYHA class ≤ 2, without signs or symptoms of heart failure or left ventricular dysfunction, after 2 hours of clinical observation were randomly allocated to treatment with PFN (600 mg p.o. as single dose) or placebo (PLA). The patients were submitted to Holter monitoring and conversion to SR was evaluated at 3 and 8 hours.

Results:	PFN (n = 119)	PLA (n = 121)
SR ≤ 3 hours	54 (45%)	22 (18%)*
SR ≤ 8 hours	91 (76%)	45 (37%)*

*$p < 0.001$

Mean conversion times to SR were for PFN 181 ± 118 min and for PLA 181 ± 112 min (NS). Adverse effects: 8 patients on PFN and 7 on PLA had